REMARKS

Claims 1-19 are currently pending in the present application.

Applicants request reconsideration of the above-identified application in view of the following remarks.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-19 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Lewin, et al., J. Med. Chem., 35(1), pp. 135-140 (1992) ("Lewin") in view of Somers et al., United States Patent 5,376,667 ("Somers"). The Examiner asserts that Lewin "discloses the synthesis of esters of benzoylecgonine by reacting ecgonine with 1,1'-carbonyldiimidazole, followed by reaction of the activated ester with an excess of alkanol and then allowing the reaction mixture to react to form the corresponding alkyl ester". Office Action, page 2. The Examiner asserts that Somers "discloses that the mono-esters of 1,2-propanediol and benzoylecgonine or ecgonine or ecgonidine are useful in treating rheumatoid arthritis." Ibid. The Examiner concludes that "one of skill wanting to produce a more concentrated version of the useful product would be motivated to use the 1,1'-carbonyldiimidazole method taught by Lewin for making mono-esters of the same carboxylic acids." Ibid. Applicants traverse.

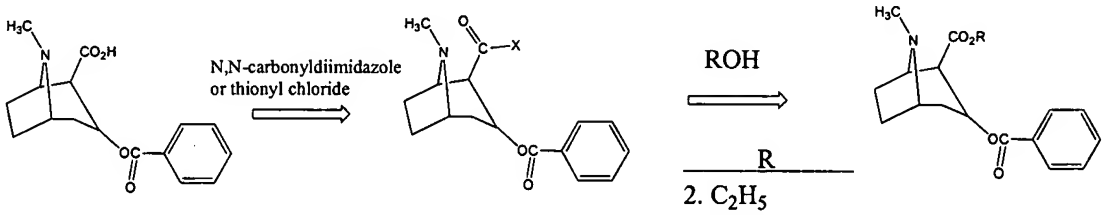
In brief, applicants' invention, as defined by claim 1, is a method for preparing a hydroxyalkyl tropane ester, comprising the steps of: (a) contacting a tropane and 1,1'-carbonyldiimidazole to produce an activated tropane ester; (b) contacting the activated tropane

ester with an excess of an alkanediol to form a reaction mixture; and (c) maintaining the reaction at a temperature and for a sufficient time for the activated tropane ester to react with the alkanediol to form the corresponding hydroxyalkyl tropane ester. As detailed below, the combination of Lewin and Somers does not teach or suggest each and every element of applicants' claimed method. Also, there is no reasonable expectation of success in preparing a hydroxyalkyl tropane ester from an alkanediol using the combined teachings of Lewin and Somers. Therefore, the Examiner has not established a prima facia case of obviousness.

Applicants' invention, as defined by claim 1, is a method for preparing hydroxyalkyl tropane esters in which "an activated tropane ester" is produced and reacted with an "excess of an alkanediol". The addition of *excess diol* to an activated tropane ester *selectively* produces a single hydroxyalkyl tropane ester in *high yield* and free from impurities that complicate or prevent efficient purification of the final product (page 7, lines 19-21 of the specification). These aspects of applicants' invention render it with superior with advantages over the prior art methods. Prior to applicants' invention, methods for preparing hydroxyalkyl tropane esters resulted in a complex *mixture* of hydroxyalkyl tropane mono-esters and diesters in *low yield*. As discussed below, the combination of Lewin and Somers fails to teach or suggest applicants' method for preparing hydroxyalkyl tropane esters.

Lewin does not teach or suggest applicants' claimed invention. Lewin teaches the synthesis of esters of benzoylecgonine. In the Lewin method, an activated tropane ester is produced and then reacted with 1.1 equivalents (i.e., a *slight* excess) of a *simple* alcohol, i.e., an

alcohol having one hydroxy group. See, for example, Method B, p. 139, col. 1. Lewin provides the following scheme illustrating its method for forming a tropane ester:



22a. X = 

b. X=Cl

2. C_2H_5
3. $(CH_2)_3CH_3$
4. $CH(CH_3)_2$
5. C_6H_5
6. $(CH_2)_3C_6H_5$
7. $CH_2C_6H_5$
8. $(CH_2)_2C_6H_5$
9. $CH_2CH{=}CHC_6H_5$
14. $(CH_2)_2(p\text{-}NO_2C_6H_4)$
15. $(CH_2)_2(p\text{-}ClC_6H_4)$

(Lewin, Scheme 1 on page 136). As shown in the Lewin scheme, a simple alcohol (indicated as R-OH), e.g., ethanol, is added to activated tropane ester 22a to produce tropane ester 2. Thus, nowhere in Lewin is there any disclosure for preparing tropane esters using an excess of an alkanediol, as required by applicants' claim 1.

The failure of Lewin to teach or suggest applicants' method is no way cured by the teaching of Somers. Somers discloses that mono-esters of 1,2-propanediol and benzoylecgonine, ecgonine or ecgonidine are useful in treating rheumatoid arthritis. Somers also discloses a method for producing compositions comprising such mono-esters. In the Somers method, a tropane is heated in a solution of alkanediol (column 7, lines 3-17 of Somers). The resulting composition contains a complex mixture of the 2-hydroxypropyl derivatives of benzoylecgonine and ecgonidine, as well as benzoylecgonine, ecgonine and

ecgonidine (Example 3, column 12, lines 40-60 of Somers). Isolation of a single hydroxypropyl tropane ester from this complex mixture is difficult and the yield is low (page 2, lines 19-20 of the specification). Indeed, the Examiner acknowledges the low yield of the Somers method in his statement that "one of ordinary skill in the art wanting a more concentrated version of the useful product" would use another method. Somers makes no mention of forming an activated ester prior to the addition of alkanediol. Thus, Somers, like Lewin, fails to teach or suggest a method for preparing hydroxyalkyl tropane esters in which an activated tropane ester is produced and reacted with an excess of alkanediol, as required by applicants' claim 1.

In addition to failing to teach or suggest the applicants' invention, the combined teachings of Lewin and Somers do not provide a reasonable expectation of success. As detailed above, Lewin discloses a method for preparing tropane esters from simple alcohols. And, Somers discloses a method for preparing a complex mixture of mono-esters of benzoylecgonine, ecgonine or ecgonidine in low yield. The skilled artisan would not reasonably expect that the 1,1' carbonyl method taught by Lewin, as concluded by the Examiner, would produce hydroxyalkyl tropane esters selectively and in high yield. To the contrary, the skilled artisan would have expected that such esterification would produce a complex mixture of primary and secondary hydroxyalkyl tropane mono-esters and diesters. See, e.g. page 2, lines 23-27 and Scheme 1, page 3 of the specification. Thus, the combination of Lewin and Somers does not provide a reasonable expectation of success because neither reference addresses or recognizes a solution to the problem of producing complex mixtures of

hydroxyalkyl tropane esters. The Examiner's conclusion amounts to nothing more than an "obvious to try" situation. "Obvious to try" is not the correct legal standard for obviousness. See, e.g., *In re O'Farrell* (7 USPQ2d 1673 (Fed Cir 1988)).

For at least the above reasons, the Examiner has not established a prima facia case of obviousness. Applicants therefore request that the Examiner withdraw the 35 U.S.C. § 103(a) rejection of claims 1-19.

Applicants request reconsideration of the above-identified application in view of the above remarks.

Respectfully submitted,

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